Kettering Medical Center

October 8, 1999

Food and Drug Administration
Dockets Management Branch
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 99N-4063
Current Good Manufacturing Practices for Positron Emission Tomography Drug Products; Preliminary Draft Regulations in the Federal Register Volume 64, No. 183, Wednesday, September 22, 1999.

Dear Sir or Madam:

Kettering Medical Center is a non-profit community hospital, we have both a dedicated scanner and a cyclotron in our clinical PET imaging center. We are not associated with a University. As the department's nuclear pharmacist I have followed the FDA's role in PET closely and I have attended the past three meetings held by the FDA regarding PET drugs. Please consider the following.

"Appropriate cGMP's for requirements for such drugs", such a simple phrase in the FDMA legislation, simple but necessary when one considers the uniqueness of PET drugs. One must constantly remind themselves of this fact when devising appropriate cGMP's. Appropriate cGMP's will mean differences from some of the current cGMP's as defined in 21 CFR. Given the uniqueness of PET drugs however these differences will not subvert or harm the process.

Subpart A--General Provisions
(o) Receiving facility, delete this definition. From the discussions at the last meeting it was clear that restrictions were not intended, however restrictions are likely to creep in regardless of the way it is defined. Its need though is questioned. A "receiving facility" would be the responsibility of the centralized nuclear pharmacy or nuclear medicine/PET imaging department that receives the PET drug prior to dispensing. This is not something that we as manufacturer's should or could control.
(r)Theoretical yield and (j) Percentage of theoretical yield, delete these definitions. Our synthetic processes are to short that it would be impractical to try to measure the yield at any "phase of production". Their use and calculation are irrelevant to the manufacturing of PET drugs.

Subpart E--Control of Components, Containers, and Closures
(c)(1) and (2) One way PET drugs are unique is with end product testing, a sample is tested from the batch which is in one container. We do not test a statistical sample of a large production synthesis. We test a sample that is 100% representative of the final product. This fact plus the incredibly short synthesis times (as compared to traditional synthesis) renders the need for traditional control and testing of components irrelevant and inappropriate. The actual time of synthesis for a PET drug can be less than the actual time it would take for "control of components" as defined by traditional methods. After ten years of preparing FDG our only synthesis failures which have been rare have come from the malfunction of valves in our synthesis unit. Following these synthesis failures our response was to prepare and carry out another synthesis using the same components in our second synthesis unit.

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Since we test the final quality of each PET drug manufactured we are assured of a safe product. An appropriate control for a PET drug component would be to require a certificate of analysis from the manufacturer. Any additional testing would be irrelevant and inappropriate.

Subpart F--Production and Process Controls
(c)(1) The name and strength should be the name and a range of strength to allow for the normal variability in the synthesis yield.
(c)(5) A statement of theoretical yield is not appropriate, use a statement of the range of end of synthesis yield.
(e) The production and dispensing area should be changed to the production area and if present the distribution area. Some locations will not distribute to other sites and hence would not have a distribution area.
(f) Process controls must include control of in-process materials..., as I understand this would require a separate log documenting whether or not we read and filed a C.O.A. on a component, if this is the case delete this requirement. This sounds like a "control of a control", it is inappropriate for PET drugs.
(h) As stated earlier we test a sample that is 100% representative of the final product, what would be the relevance of testing a sample 30 days later? In essence this would establish a expiration or stability time of 30 days to ensure that a sample tested 30 days later would still pass the initial quality control tests. This is inappropriate for PET drugs, delete this paragraph.

Subpart G--Laboratory Controls
(g)(1) For in house testing this requirement is inappropriate. Given the fact that we will try to release these products before they decay away testing in almost every case will be performed immediately. Only for samples tested at a off site location such as for 2-chloro-2-deoxy-D-glucose would recording the date, volume and batch number of the sample be appropriate.

Subpart J--Distribution
(a) Dispensing and control of the PET drug should not be mixed with the manufacturing of the PET drug. Dispensing should be performed in the same manner that other radiopharmaceuticals are now. That is they are dispensed by a pharmacist at a centralized nuclear pharmacy or by a nuclear medicine technologist under the supervision of a physician in a nuclear medicine/PET department. No manufacturer sees the final prescription before their product is used. The control and responsibility of the prescription resides with the individual dispensing the product. The uniqueness of PET drugs is in their manufacturing. The dispensing of them is not unique from radiopharmaceuticals.
(b)(3) Delete, see above justification.

Model Application for FDG
8. Controls for the Finished Dosage Form:
Radionuclidic Identity; instead of specifying a dose calibrator list a "suitable radioactivity detector" to allow for other instruments which would be able to perform this measurement.

Microbiological Validation of Sterilization and Sterility Assurance: These appear to be written specifically based on the experience at Peoria. Since the Peoria approval other FDG synthesizer units have come into use such as the one supplied by Nuclear Interface. This new version of a synthesizer units does not use new vials with each synthesis, rather their reagent supply vessels are permanent and new additions are made through a septum. They have permanent transfer lines and do not rely on stopper sets. The new units offer a big improvement over the old style CPCU's in use at Peoria. The new synthesizer units offer computer aided manufacturing, are easier to set up, offer a closed system and are much more reliable.

- Radiopharmacy Environmental Controls. "...and the synthesis unit should be near the aseptic hood. "It is recommended that batch records indicate that components, materials and equipment be in protective wrapping or containers when transferred to the aseptic area, ...". I'm not sure what this means or even how it would be accomplished. Some components such as a sterile syringe, sterilizing filter or IV tubing would be in its original protective package.

Other components such as triflate are weighed out in the open on a analytical balance and transferred to a vial. The above requirement sounds like it is beyond what is actually happening now at the approved site in Peoria. The intent of this section may be more appropriate if the phrase is edited to the following, "It is recommended that *master* batch records indicate *when appropriate* that components, materials and equipment be in protective wrapping or containers when transferred to *or from* the aseptic area,..." This will allow for the proper flexibility as to when to require needed protective wrapping or containers for components.

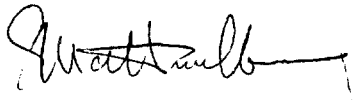
- The Aseptic Hood. With the use of the new synthesizer units set-up does not take place in an aseptic hood. Likewise the set-up at Peoria does not take place in a aseptic hood. Is this intended to be a new requirement for the set-up for a synthesis? If so, it is inappropriate and has been proven to be unnecessary.

- If the aseptic hood's function is for the assembly of the final product collection vial this requirement and its associated tests for microbiological and airborne particle are inappropriate for PET drugs. If one were preparing these vials from empty glass vials, rubber septums and aluminum seals then these steps would be appropriate. For PET drugs we use aseptic technique and insert needles (vent and sterilizing filters) through a septum in a pre-prepared sterile empty vial for our final collection vials. This vial can be and usually is prepared within a few minutes of starting the synthesis. This is not a vial assembly which sits in storage for weeks, months before it is actually used. Each synthesis uses only one collection vial. The appropriate use of a aseptic hood in a PET drug manufacturing site is to try to maintain manufacturing conditions as clean as reasonably possible (ACARA, my apologies to the NRC). Given the nature of the chemistry of our synthesis, the length of our synthesis , the short shelf life of our product measured in hours (not days, weeks or months) and the fact that we use a sterile closed collection system one can argue that the use of an aseptic hood is beyond minimum requirements for PET drugs. This has been proven at Peoria where an aseptic hood is only used to insert needles/filter assemblies through a septum of a sterile collection vial, hardly a high or even low risk procedure. If the use of an aseptic hood does become a requirement, a six month evaluation of its air flow and microbiological performance would be appropriate for its use in the manufacturing of PET drugs.

- The requirements for aseptic technique, filtration process qualification and finished product microbiological testing are appropriate and exceed the minimum requirements for PET drugs.

Given the uniqueness of the PET drug manufacturing process and the mandate of FDMA for the FDA to develop appropriate regulations this certainly make for interesting times. I thank you in advance for your consideration of these comments.

Sincerely,



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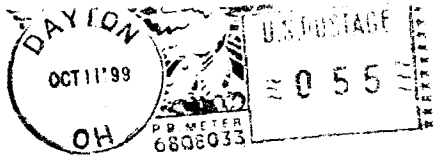

FROM:

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FORM SVB 941-046

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